

Research Article

Febuxostat and Cardiovascular Events: A Systematic Review and Meta-Analysis

John A. Cuenca ¹, Javier Balda,¹ Ana Palacio,^{2,3} Larry Young,^{3,4} Michael H. Pillinger,^{5,6} and Leonardo Tamariz ^{2,3}

¹Universidad Catolica de Santiago de Guayaquil, Ecuador

²Division of Population Health and Computational Medicine, Miller School of Medicine, University of Miami, Miami, FL, USA

³Veterans Affairs Medical Center, Miami, FL, USA

⁴Division of Rheumatology, University of Miami, USA

⁵Division of Rheumatology, New York University School of Medicine, USA

⁶Veterans Affairs Medical Center, New York, NY, USA

Correspondence should be addressed to Leonardo Tamariz; ltamariz@med.miami.edu

Received 2 November 2018; Revised 3 January 2019; Accepted 16 January 2019; Published 3 February 2019

Academic Editor: Tim Jansen

Copyright © 2019 John A. Cuenca et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Febuxostat is approved in the United States for the management of hyperuricemia in patients with gout. In November 2017 the FDA released a warning alert on a possible link between febuxostat and cardiovascular disease (CVD) reported in a single clinical trial. **Objective.** To conduct a systematic review and meta-analysis and assess the risk of major adverse cardiovascular events (MACE) in patients receiving febuxostat compared to a control group. **Methods.** We searched the MEDLINE and EMBASE database for studies published up until March 2018. We included randomized clinical trials (RCTs) that compared febuxostat to control groups including placebo and allopurinol. We calculated the pooled relative risk (RR) of MACE and cardiovascular disease (CVD) mortality with the corresponding 95% confidence intervals (CI). **Results.** Our search yielded 374 potentially relevant studies. Among the 25 RCTs included in the systematic review, 10 qualified for the meta-analysis. Among the 14,402 subjects included, the median age was 54 years (IQR 52–67) and 90% were male (IQR 82–96); 8602 received febuxostat, 5118 allopurinol, and 643 placebo. The pooled RR of MACE for febuxostat was 0.9; 95% CI 0.6–1.5 ($p=0.96$) compared to the control. The RR of CV-related death for febuxostat was 1.29; 95% CI 1.01–1.66 ($p=0.03$). **Conclusions.** Compared with other SU-lowering treatments, febuxostat does not increase or decrease the risk of cardiovascular disease but may increase the risk of CVD death. More RCTs measuring cardiovascular safety as a primary outcome are needed to adequately evaluate the risk of CVD with febuxostat.

1. Introduction

Gout is an independent predictor of cardiovascular diseases [1] and serum urate (SU) is associated with the incidence of atrial fibrillation [2, 3], heart failure mortality [4], coronary artery disease calcification [5], and other cardiovascular diseases. However, improving cardiovascular clinical outcomes by reducing SU is controversial [6, 7].

Febuxostat is a nonpurine-like xanthine oxidase inhibitor used in the management of hyperuricemia. Studies have shown no inferiority in reducing SU compared to allopurinol, the most commonly used SU-lowering agent [8]. However, on

November 15, 2017, the FDA issued an alert regarding febuxostat [9] based on preliminary results of the CARES trial, conducted in over 6000 patients to assess the cardiovascular safety of febuxostat compared with allopurinol. The full study was subsequently published [10] and showed no difference in overall cardiovascular events, but an increased risk of all-cause and cardiovascular mortality in the febuxostat group.

Twelve systematic reviews or meta-analysis have been published about SU-lowering therapy and gout or hyperuricemia. Six evaluated the efficacy of medications with no mention of cardiovascular events [8, 11–15], three evaluated their renoprotective effects [16–18], one evaluated the effect

of SU-lowering therapy on cardiovascular prevention [7], and one evaluated the effect of SU-lowering therapy on the effects on blood pressure [19]. Only one meta-analysis [20] evaluated the cardiovascular events of febuxostat and found no excess events; however, this study did not include CARES, only searched in one database to identify cardiovascular events as adverse events, and only included four studies.

To evaluate the available evidence regarding the cardiovascular safety of febuxostat, we performed a systematic review and meta-analysis of studies comparing hyperuricemic subjects with and/or without gout receiving febuxostat, other SU-lowering therapies, or placebo.

2. Materials and Methods

2.1. Protocol and Registration. We performed our systematic review according to the Cochrane methodology. The protocol of the present study was not registered. Our report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

2.2. Search Strategy. We conducted a literature search using the MEDLINE database through PubMed from inception to 2018. We filtered all articles, except for those containing key terms such as hyperuricemia and febuxostat. We used the following search terms: "febuxostat"[MeSH Terms] OR "febuxostat"[All Fields]) AND ("hyperuricaemia"[All Fields] OR "hyperuricemia"[MeSH Terms] OR "hyperuricemia"[All Fields]) OR "Gout"[Mesh] AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp]) AND "humans"[MeSH Terms]). We conducted all searches in March 2018 and supplemented the initial results with manual searches of bibliographies of key relevant articles. In addition, we also searched the EMBASE database using the same timeframe and criteria as well as a search of the clinical trials.gov database for unpublished studies or data on CV events not reported in the original publication. We excluded conference abstracts and articles not published in English because of inability to obtain all the necessary information.

2.3. Inclusion and Exclusion Criteria. We included randomized clinical trials that compared febuxostat to one or more control groups, reported adverse events including cardiovascular events, had a follow-up period of any length, and were published in English. We excluded reviews, cohort and cross-sectional studies, and case reports.

2.4. Selection Criteria. Two investigators (JC and JB) reviewed the abstract of each citation and identified abstracts for full-text review. When either selected an article for full-text review, it was evaluated by both investigators. Agreement on whether to examine the full text or to incorporate the article in the evidence table was calculated by using interrater agreement.

2.5. Data Collection. One investigator (JC) was responsible for completing the evidence table and a second investigator

(JB) verified the accuracy of the data collected. Differences between the two final reviewers were resolved by consensus with the senior investigator (LT). From each study we collected the population, indication for the use of SU-lowering medications, demographics, concomitant medications used in the trial, follow-up time, the prevalence of CV risk factors, the number of gout flares, and the incidence of CV events during the follow-up period.

2.6. Qualitative Analysis. Because we included only randomized controlled trials we used the 11-item Critical Appraisal Skills program checklist to evaluate the quality of each study [45]. To better describe possible sources of bias, we report on key quality metrics: concealment of allocation, loss to follow-up, cross-over, intention to treat analysis, success of randomization, sample size calculation, missing data, recall bias, and measurement bias. Two investigators were responsible for completing the quality evaluation (JC and JB). Differences between the reviewers were resolved by consensus (led by LT) and we calculated interrater agreement.

2.7. Medication Groups. Our main medication of interest was febuxostat. We compared the effect of febuxostat to control groups defined as placebo, allopurinol or other SU-lowering drugs including topiroxostat and benzbromarone. The rationale for grouping placebo and all other medications as one control group was because of the small number of placebo controlled trials (n=4); however we did conduct a sensitivity analysis including only studies that compared febuxostat and placebo. We did not include lesinurad in our analyses, as it is approved only for use with allopurinol or febuxostat and we could not evaluate the individual effect of the medication. To evaluate whether febuxostat dosage was associated with CV events, we classified all studies as either high dose (≥ 80 mg) or low dose (< 80 mg). We selected this cutoff as a previous meta-analysis on the efficacy of the medication used the same cutoffs [8].

2.8. Primary and Secondary Outcome. Our primary outcome was major adverse cardiovascular events (MACE). We defined MACE as nonfatal myocardial infarction (MI), angina pectoris, heart failure, ischemic coronary artery disorders, and cardiovascular related deaths [21]. To evaluate the impact of febuxostat on individual outcomes we conducted an analysis on secondary outcomes defined as ischemic heart disease (including unstable angina with coronary revascularization), nonfatal myocardial infarction, and CV-related death.

For our quantitative analysis we only included 10 studies that reported either the primary or secondary outcome we defined previously; the remaining studies were not included in the quantitative analysis.

2.9. Subgroup Analysis. To evaluate if the results were impacted by confounders we collected the following information from each study: the study included hyperuricemic patients or only gout patients; concomitant medications that could affect the cardiovascular risk [46] like nonsteroidal anti-inflammatories (NSAIDs) and aspirin; baseline

cardiovascular risk including coronary artery disease and cardiovascular risk factors; and the number of gout flares in the febuxostat group as a marker of inflammation. We defined a study as evaluating gout if all patients included in the study had gout and we defined hyperuricemia as those studies that included subjects based on elevations of SU only. We also reported the timing of the cardiovascular (CV) events by study.

2.10. Statistical Analysis. We reported relevant baseline characteristics as median values with the interquartile range (IQR). To assess for heterogeneity across studies, we used the Cochran Q chi-square statistic and the I-squared statistic. We defined heterogeneity as an I-squared greater than 50%.

For the quantitative analysis we used Stata 14 (StataCorp LP, College Station, TX). We evaluated publication bias using the Egger's method. We calculated the pooled relative risk (RR) of the primary and secondary outcome with the respective 95% confidence intervals (CIs) for febuxostat compared to the control arm using the fixed effects method.

We also conducted metaregression for the primary and secondary outcome as the dependent variable [47] and then calculated the exponentiated beta-coefficient using the random effects model and included baseline cardiovascular risk, follow-up time, gout versus hyperuricemia, NSAID or aspirin use, and the number of gout flares in the model.

3. Results

3.1. Literature Search. Figure 1 shows the flowchart of included and excluded studies. Our search yielded 374 abstracts from PubMed, 110 from EMBASE, and 18 protocols from the clinicaltrials.gov database. From a total of 502 citations we removed 91 duplicate abstracts. We excluded 358 studies at the abstract level and selected 53 for full-text review; of these we excluded 28. Therefore, 25 studies were finally included. Interrater agreement between reviewers on inclusion versus exclusion of studies was 100%. From the clinicaltrials.gov register, we retrieved additional cardiovascular events data for 5 of the 25 published studies [25, 38–41]. Among the 25 included studies, 10 reported MACE and 15 reported no CV events during the study follow-up.

3.2. Baseline Characteristics. Table 1 shows the baseline characteristics of the 25 studies included in the qualitative review. The studies included 14,402 participants with hyperuricemia: 8,602 (59%) received febuxostat, 5,118 (36%) allopurinol, and 643 (4%) placebo. The median age of the trial participants was 54 years (IQR 52–67) and 90% (IQR 82–96) were male. The median follow-up of the studies was 6 months (IQR 2.7–12), 53% (IQR 43–92) had hypertension, and 32% (IQR 11–38) had diabetes.

Studies that reported CV events had a median follow-up of 12 months (IQR 6.4–24) compared to studies that reported no CV events in which the median follow-up was 3.6 months (IQR 1.8–6). Nine of the 15 studies that reported no CV events evaluated febuxostat on several cardiovascular conditions.

Only ten of the studies were exclusively conducted in North America. Twelve of the studies compared febuxostat

to allopurinol. The remaining studies compared febuxostat to placebo (10), to both placebo and allopurinol (1), to topiroxostat (n=1), and to benzbromarone (n=1).

Eleven studies included patients with gout exclusively, 5 recruited patients with hyperuricemia and no evidence of gout, and the remaining 9 studies included patients with cardiovascular diseases.

3.3. Qualitative Evaluation. The beta-coefficient for publication bias was 0.30; 95% CI -0.81–1.42, $p=0.53$. Our qualitative evaluation found that all but three studies were blinded. Outcomes other than SU were infrequently reported, particularly in short follow-up studies designed to evaluate safety of febuxostat on patients with CV risk factors. The CARES trial was the only study designed to evaluate the long-term cardiovascular safety of febuxostat as the main endpoint. Despite its relevance, the CARES trial had a significant limitation, almost 57% of patients discontinued the trial treatment prematurely, and 45% of the participants did not complete follow-up which could have caused a considerable impact on the results. However, the number of participants who discontinued the trial and did not complete the follow-up was similar in both arms of the study.

3.4. Association between Febuxostat and MACE. Ten studies (Table 2) reported the association between febuxostat and MACE [10, 21, 22, 32, 38–41, 43, 44]. Nine of these studies included patients with a recorded history of either hypertension, heart failure, or coronary artery disorder, whereas the CARES trial had the higher proportion. Figure 2 shows the association between febuxostat and MACE compared to control groups. The RR of MACE for any febuxostat dosage was 1.06; 95% CI 0.92–1.23 ($p=0.42$) with an I-squared of 0%. The RR of MACE for any febuxostat dosage when the control group was placebo was 1.81; 95% CI 0.72–4.53 ($p=0.20$). The RR of MACE for low dose febuxostat dosage was 1.03; 95% CI 0.65–1.66 ($p=0.43$). The RR of MACE for high dose febuxostat dosage was 0.98; 95% CI 0.47–2.04 ($p=0.97$). Only two studies reported the timing of the CV events and most of them occurred within 24 months of exposure to the medication.

3.5. Association between Febuxostat and the Secondary Outcome. Six studies reported the secondary outcome [10, 21, 38, 39, 41, 44]. The RR of CV-related death for febuxostat was 1.29; 95% CI 1.01–1.66, $p=0.03$. When the largest study (CARES) [10] was excluded, the RR of CV death for febuxostat was 0.73; 95% CI 0.24–2.25, $p=0.64$.

3.6. Subgroup Analysis. For the primary outcome, one has the following: the metaregression beta-coefficients for gout (1.63), number of gout flares (1.00), coronary artery disease (1.00), follow-up time (1.00), NSAID (0.99), and aspirin (1.00), all with a p -value >0.05 . For the secondary outcome, one has the following: the metaregression beta-coefficients for coronary artery disease (1.70), number of gout flares (1.00), follow-up time (1.00), NSAID (1.02), and aspirin (0.98), all with a p -value >0.05 .

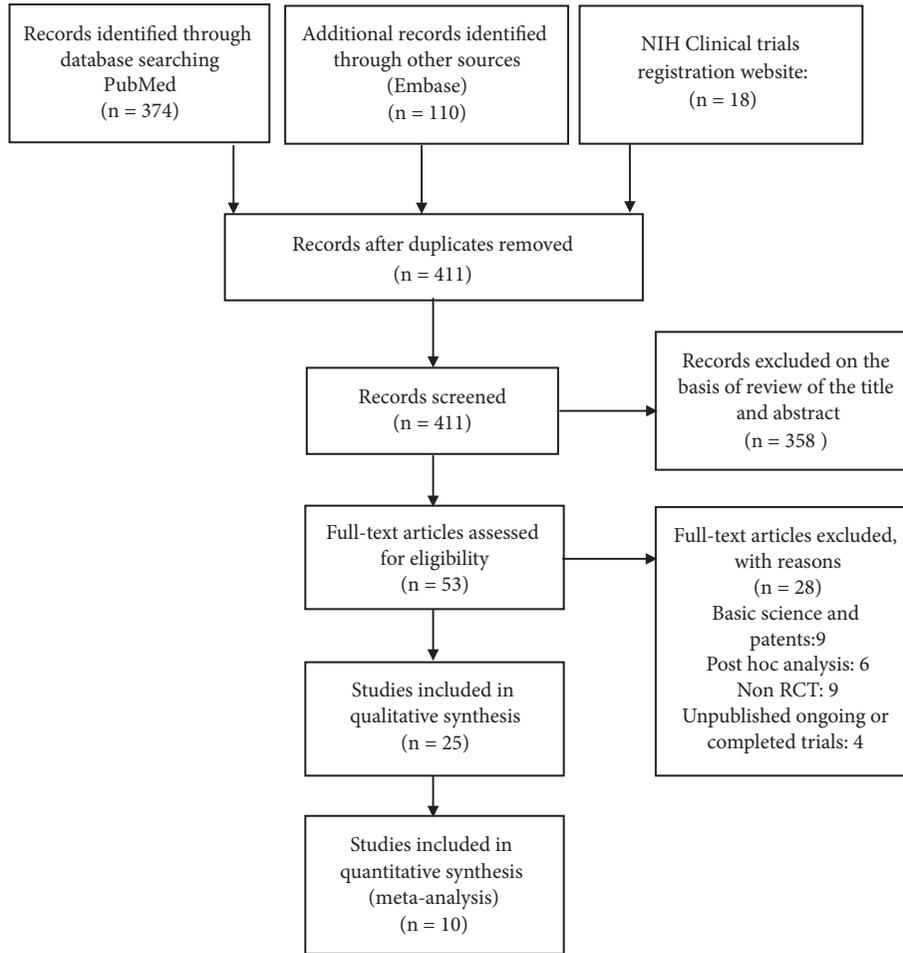


FIGURE 1: Flowchart of included studies. NIH: National Institutes of Health. RCT: randomized clinical trial.

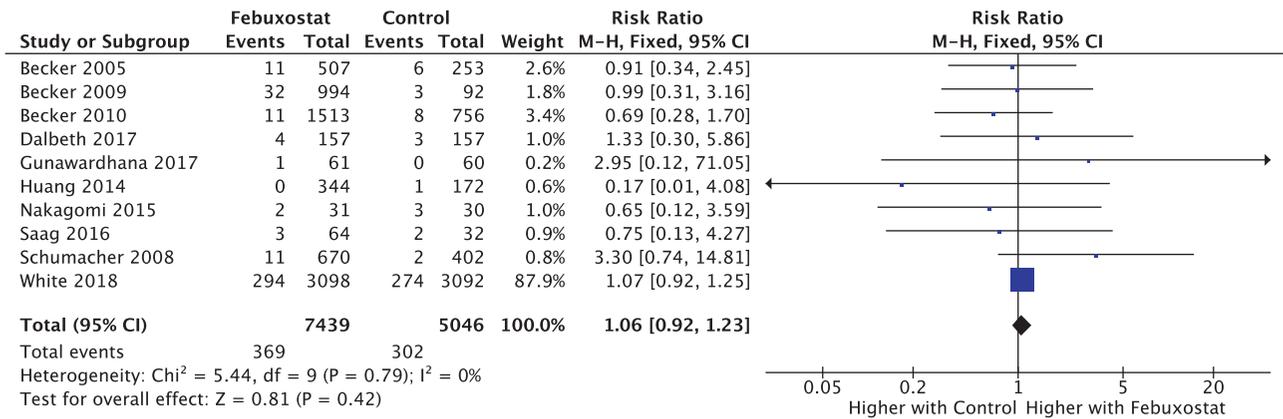


FIGURE 2: Forest plot of the association between MACE and febuxostat.

4. Discussion

Our study found that febuxostat does not increase the overall risk of major adverse cardiovascular events among patients with gout and hyperuricemia. However, our analysis also showed an increased the risk of cardiovascular death with

febuxostat. We did not find that CAD, NSAID or aspirin use, number of gout flares, or including only gout patients were factors related to the excess cardiovascular death.

Elevated SU is associated with increasing heart failure incidence [48, 49], heart failure mortality [4], incident hypertension [50], incident atrial fibrillation [3], and ischemic

TABLE 1: Baseline characteristics.

Author	Country	Population	n	Age (SD)	Males %	Intervention	Control group	Follow up (m)	Industry funding	Gout	HTN	CAD	HF	T2DM
White [10]	US	Gout + previous CV events	6190	65 IQR (58-71)	84	FBX 40 mg up to 80 mg	Allopurinol	32	Yes	100	92	76	-	20
Dalbeth [21]	US	Gout	314	51 (+/-12)	92	FBX 40 mg/ 60 mg/ 80 mg	Placebo	24	Yes	100	-	-	-	-
Gunawardha [22]	US	HTN	121	54 (+/-10.6)	81	FBX 80 mg	Placebo	1.5	Yes	-	100	-	-	-
Sezai [23]	Japan	CVD	55	68 (+/-9)	83	FBX 60 mg	Topiroxostat	12	Yes	-	82	36	-	35
Ohta [24]	Japan	HTN	20	64 (+/-12)	90	FBX 40 mg	Benzbromarone	9	No	-	100	-	-	-
Beddhu [25]	US	CKD T2DM	80	68 (+/-10)	65	FBX 80 mg	Placebo	5.5	Yes	-	77	18	10	100
K-H [26]	China	Gout	109	45 (+/-11.5)	97	FBX 80 mg	Allopurinol	2.7	Yes	100	-	-	-	-
Sircar [27]	India	CKD	108	57 (+/-12.6)	70	FBX 40 mg	Placebo	6	Yes	-	98	38	-	38
Tani [28]	Japan	HTN	60	67 (+/-12)	88	FBX 20 mg	Placebo	6	No	-	100	32	-	32
Tanaka [29]	Japan	CKD	45	68 (+/-8.2)	88	FBX 40 mg	Allopurinol	2.7	No	-	43	-	-	-
Tsuruta [30]	Japan	ESRD	53	68 (+/-12.55)	64	FBX 10 mg	Placebo	1	No	-	79	27	-	42
Xu [31]	China	Gout	504	47 (+/-11.5)	95	FBX 40 mg/ 80 mg	Allopurinol	5.5	Yes	100	16	-	-	5
Huang [32]	China	Gout	512	47 (+/-11.2)	98	FBX 40 mg/ 80 mg	Allopurinol	6.4	Yes	100	28	-	-	-
Sezai [33]	Japan	Cardiac surgery	141	67 (+/-10.3)	82	FBX 60 mg	Allopurinol	6	No	-	81	40	-	36
Katamani [34]	Japan	Hyperuricemia	40	54 (+/-10.4)	100	FBX 40 mg/ 60 mg	Allopurinol	3.6	Yes	76	42	-	-	5
Katamani [35]	Japan	Hyperuricemia	202	53 (+/-12.7)	97	FBX 20 mg/ 40 mg/ 60 mg/ 80 mg	Placebo	3.6	Yes	59	49	-	-	11
Katamani [36]	Japan	Hyperuricemia	102	48 (+/-13.6)	100	FBX 20 mg/ 40 mg	Placebo	1.8	Yes	49	35	-	-	11
Katamani [37]	Japan	Hyperuricemia	244	52 (+/-13.5)	98	FBX 40 mg	Allopurinol	1.8	Yes	47	33	-	-	10
Becker [38]	US	Gout	2269	52 (+/-11.7)	94	FBX 40 mg/ 80 mg	Allopurinol	6	Yes	100	53	-	-	14
Becker [39]	US	Gout	1086	51 (+/-11.6)	96	FBX 80 mg/ 120 mg	Allopurinol	40	Yes	100	45	-	-	7
Schumacher [40]	US	Gout	1072	52 (+/-12.2)	94	FBX 80 mg/ 120 mg/ 240 mg	Allopurinol and placebo	6.4	Yes	100	47	-	-	-
Becker [41]	US	Gout	762	52 (+/-12.1)	96	FBX 80 mg/ 120 mg	Allopurinol	12	Yes	100	44	10	-	7
Becker [42]	US	Gout	153	54 (+/-12.6)	89	FBX 40 mg/ 80 mg/ 120 mg	Placebo	1	Yes	100	49	60	-	13
Nakagomi [43]	Japan	HF+Hyperuricemia	61	70.5 (+/-9)	70	FBX 40 mg	Allopurinol	12	No	-	93	72	100	34
Saag [44]	US	Gout+CKD	96	65.7 (+/-10)	80	FBX up to 80 mg	Placebo	12	Yes	100	95	-	-	44

n: number of participants. HTN: hypertension. CAD: coronary artery disease. HF: heart failure. T2DM: type 2 diabetes mellitus. CV events: cardiovascular events. CKD: chronic kidney disease. ESRD: end-stage renal disease. SD: standard deviation. IQR: interquartile range. FBX: febuxostat.

TABLE 2: Major adverse cardiac events.

Author	Drug	n	Angina pectoris	HF	Ischemic Coronary artery disorder	Non-fatal MI	CV death	MACE
Dalbeth [21]	FBX 40 mg	157	0	1	1	1	1	4
	Placebo	157	0	1	1	0	1	3
Gunawardhana [22]	FBX 80 mg	61	0	0	1	0	0	1
	Placebo	60	0	0	0	0	0	0
Huang [32]	FBX 40 mg	172	0	0	0	0	0	0
	FBX 80 mg	172	0	0	0	0	0	0
	Allopurinol	172	1	0	0	0	0	1
	Placebo	172	0	0	0	0	0	0
Becker [38]	FBX 40 mg	757	2	2	4	0	0	8
	FBX 80 mg	756	0	0	2	1	0	3
	Allopurinol	756	0	1	4	1	2	8
Becker [39]	FBX 80 mg	606	0	3	17	0	4	24
	FBX 120 mg	388	0	3	3	0	2	8
	Allopurinol	92	0	1	2	0	0	3
Schumacher [40]	FBX 80 mg	267	0	0	3	0	0	5*
	FBX 120 mg	269	0	0	2	0	0	5*
	FBX 240 mg	134	0	0	0	0	0	1*
	Allopurinol	268	0	0	0	0	0	1*
Becker [41]	FBX 80 mg	256	0	3	3	0	1	7
	FBX 120 mg	251	0	1	2	0	1	4
	Allopurinol	253	0	0	6	0	0	6
Nakagomi [43]	FBX 40	31	0	0	2	0	0	2
	Allopurinol	30	0	0	3	0	0	3
Saag [44]	FBX 30 mg BID	32	0	1	0	0	0	1
	FBX 48/80 mg QD	32	0	1	0	0	1	2
White [10]	FBX up to 80	3098	0	0	49	111	134	294
	Allopurinol	3092	0	0	56	118	100	274

FBX: febuxostat; HF: heart failure; MACE: major adverse cardiovascular events. *Reported as cardiovascular events (chest pain, coronary artery disease, myocardial infarction, and atrial fibrillation), not specified how many of each.

heart disease [51]. This finding has made SU a therapeutic target to improve cardiovascular outcomes by modifying the nitroso/redox balance; however, allopurinol has not improved outcomes in heart failure [6, 52]. Therefore, there is a need for newer medications that can affect the nitroso/redox balance.

The FDA required Takeda Pharmaceuticals [9], to conduct a cardiovascular safety clinical trial based on clinical trial results [39, 40] and observational data [53] showing a possible excess in cardiovascular events before its approval in 2009. On November 2017, the FDA released a safety alert based on the results of the Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout trial (CARES trial). The study had a randomized double-blind design and included patients with gout and a history of major cardiovascular disease and found no increase in the primary outcome of MACE, defined in this RCT as CV-related death, nonfatal MI, nonfatal stroke, and unstable angina requiring urgent revascularization, but found an increase in the risk of the secondary endpoints of cardiovascular death and death from all causes in intention to treat and per protocol analyses. Due to the CARES specific design and being the only RCT published focused on measuring the febuxostat cardiovascular safety, it constitutes over 80% of our pooled analysis.

There are several potential explanations for our findings and those of the CARES trial. First, the use of NSAIDs has been associated with increasing rates of cardiovascular outcomes [54], and it is possible that NSAID use for gout prophylaxis and/or treatment may have skewed the data. While we did not observe an NSAID effect, NSAIDs were not well documented in the included studies and may have had unmeasured effects. Second, gout flares and the inflammation they entail have been associated with myocardial infarction [55]. However, in CARES, NSAID use and gout flares were similar between those using febuxostat and allopurinol. Colchicine, which has been suggested to lower rather than raise cardiovascular risk, is also used for both gout prophylaxis and acute treatment, but the data available in the studies did not permit rigorous analysis of whether colchicine use could have biased our outcomes. Third, xanthine oxidase inhibition could disrupt the activity of nitric oxide synthase [56] which can in turn reduce the coronary blood flow and cause ineffective excitation contraction myocardial coupling [6, 56]. Paradoxically, however, urate itself has also been shown to inhibit the ability of endothelial cells to secrete nitric oxide [57, 58]. The nature of our meta-analysis did not permit us to assess the impact and balance of the relative effects of nitric oxide inhibition and SU-lowering on coronary blood flow.

Our study also found that several studies were conducted in different CV at risk populations but had short follow-up and they were unable to identify CV events. All of these studies were funded by the makers of febuxostat. Typically, phase 2 and 3 studies can identify common safety issues but may not be of sufficient scope or duration to identify important but less common events.

The present study was unable to identify a profile of risk since factors included in our metaregression analysis were nonsignificant. However, the highest coefficients of risk were

seen with the presence of coronary artery disease at baseline and with those studies that exclusively tested febuxostat on gout patients.

The strengths of our study include the extensive search for cardiovascular events, the inclusion only of randomized clinical trials, the number of studies, and the evaluation of potential explanations for the excess risk.

Despite the strengths, our study has important limitations that deserve to be mentioned. First, despite having a considerably high number of studies and patients within those studies, the number of MACE or any cardiovascular event was low in both groups. This could be explained by a low incidence of risk or by the fact that cardiovascular safety was not the primary endpoint in all but one of the included trials [10], along with the short follow-up of most studies. Second, the exclusion criteria in some studies prevented patients with a history of cardiovascular disease to enter in their studies, thus reducing the patients at risk of developing MACE. Third, not all studies consistently reported the data about NSAID and aspirin use and the cardiovascular level of risk of the included patients, therefore, limiting or metaregression. Fourth, our findings of increasing CV-related death were driven by the large sample size and event rate of the CARES trial [10]. Finally, the potentially important question raised by the CARES trial, of whether febuxostat may independently increase risk of CV-related death or decrease the risk of CV-related death but to a lesser extent than allopurinol, could not be determined, given our methodology and the available data.

In conclusion, our meta-analysis of available studies indicates that while febuxostat neither increases nor decreases the risk of major adverse cardiovascular outcomes in hyperuricemic patients, it may increase the risk of CV-related death in patients with gout and a history of prior CV events. Given the high prevalence and the chronic nature of gout, caution is appropriate when deciding whether to use febuxostat in high-risk CV patients. More RCTs measuring cardiovascular safety as a primary outcome are needed to adequately evaluate the risk of CVD with febuxostat.

Data Availability

The data points used to support the findings of this study are included within the article.

Conflicts of Interest

Michael H. Pillinger serves and/or has served as a consultant for AstraZeneca, Crealta, Horizon, Ironwood, Pfizer, and SOBI and has been an investigative site for the CARES trial, sponsored by Takeda.

Acknowledgments

Michael H. Pillinger received support from a CTSA Award (1UL1TR001445) to New York University from the National Center for the Advancement of Translational Science, National Institutes of Health.

References

- [1] H. K. Choi and G. Curhan, "Independent impact of gout on mortality and risk for coronary heart disease," *Circulation*, vol. 116, no. 8, pp. 894–900, 2007.
- [2] L. Tamariz, F. Hernandez, A. Bush, A. Palacio, and J. M. Hare, "Association between serum uric acid and atrial fibrillation: A systematic review and meta-analysis," *Heart Rhythm*, vol. 11, no. 7, pp. 1102–1108, 2014.
- [3] L. Tamariz, S. Agarwal, E. Z. Soliman et al., "Association of serum uric acid with incident atrial fibrillation (from the atherosclerosis risk in communities [ARIC] study)," *American Journal of Cardiology*, vol. 108, no. 9, pp. 1272–1276, 2011.
- [4] L. Tamariz, A. Harzand, A. Palacio, S. Verma, J. Jones, and J. Hare, "Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis," *Congestive Heart Failure*, vol. 17, no. 1, pp. 25–30, 2011.
- [5] J. E. Jun, Y.-B. Lee, S.-E. Lee et al., "Elevated serum uric acid predicts the development of moderate coronary artery calcification independent of conventional cardiovascular risk factors," *Atherosclerosis*, vol. 272, pp. 233–239, 2018.
- [6] L. Tamariz and J. M. Hare, "Xanthine oxidase inhibitors in heart failure: where do we go from here?" *Circulation*, vol. 131, no. 20, pp. 1741–1744, 2015.
- [7] M. Bredemeier, L. M. Lopes, M. A. Eisenreich et al., "Xanthine oxidase inhibitors for prevention of cardiovascular events: A systematic review and meta-analysis of randomized controlled trials," *BMC Cardiovascular Disorders*, vol. 18, no. 1, p. 24, 2018.
- [8] L. I. Faruque, A. Ehteshami-Afshar, N. Wiebe, L. Tjosvold, J. Homik, and M. Tonelli, "A systematic review and meta-analysis on the safety and efficacy of febuxostat versus allopurinol in chronic gout," *Seminars in Arthritis and Rheumatism*, vol. 43, no. 3, pp. 367–375, 2013.
- [9] U S Food and Drug Administration (FDA), "Uloric (febuxostat): Drug Safety Communication - FDA to Evaluate Increased Risk of Heart-related Death," 2018.
- [10] W. B. White, K. G. Saag, M. A. Becker et al., "Cardiovascular safety of febuxostat or allopurinol in patients with gout," *The New England Journal of Medicine*, vol. 378, no. 13, pp. 1200–1210, 2018.
- [11] C. Borghi and F. Perez-Ruiz, "Urate lowering therapies in the treatment of gout: a systematic review and meta-analysis," *European Review for Medical and Pharmacological Sciences*, vol. 20, pp. 983–992, 2016.
- [12] I. Castrejon, E. Toledano, M. P. Rosario, E. Loza, F. Pérez-Ruiz, and L. Carmona, "Safety of allopurinol compared with other urate-lowering drugs in patients with gout: a systematic review and meta-analysis," *Rheumatology International*, vol. 35, no. 7, pp. 1127–1137, 2015.
- [13] S. Li, H. Yang, Y. Guo et al., "Comparative efficacy and safety of urate-lowering therapy for the treatment of hyperuricemia: a systematic review and network meta-analysis," *Scientific Reports*, vol. 6, no. 1, Article ID 33082, 2016.
- [14] J. H. Tayar, M. A. Lopez-Olivo, and M. E. Suarez-Almazor, "Febuxostat for treating chronic gout," *Cochrane Database of Systematic Reviews*, vol. 11, Article ID CD008653, 2012.
- [15] P. Ye, S. Yang, W. Zhang et al., "Efficacy and tolerability of febuxostat in hyperuricemic patients with or without gout: a systematic review and meta-analysis," *Clinical Therapeutics*, vol. 35, no. 2, pp. 180–189, 2013.
- [16] T. Kanji, M. Gandhi, C. M. Clase, and R. Yang, "Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis," *BMC Nephrology*, vol. 16, p. 58, 2015.
- [17] S. Kim, H.-J. Kim, H.-S. Ahn et al., "Renoprotective effects of febuxostat compared with allopurinol in patients with hyperuricemia: A systematic review and meta-analysis," *Kidney Research and Clinical Practice*, vol. 36, no. 3, pp. 274–281, 2017.
- [18] X. X. Zeng, Y. Tang, K. Hu et al., "Efficacy of febuxostat in hyperuricemic patients with mild-to-moderate chronic kidney disease," *Medicine (Baltimore)*, vol. 97, no. 13, p. e0161, 2018.
- [19] L.-H. Qu, H. Jiang, and J.-H. Chen, "Effect of uric acid-lowering therapy on blood pressure: systematic review and meta-analysis," *Annals of Medicine*, vol. 49, no. 2, pp. 142–156, 2017.
- [20] T. Zhang and J. E. Pope, "Cardiovascular effects of urate-lowering therapies in patients with chronic gout: A systematic review and meta-analysis," *Rheumatology (Oxford)*, vol. 56, no. 7, pp. 1144–1153, 2017.
- [21] N. Dalbeth, K. G. Saag, W. E. Palmer et al., "Effects of febuxostat in early gout: a randomized, double-blind, placebo-controlled study," *Arthritis & Rheumatology*, vol. 69, no. 12, pp. 2386–2395, 2017.
- [22] L. Gunawardhana, L. McLean, H. A. Punzi et al., "Effect of febuxostat on ambulatory blood pressure in subjects with hyperuricemia and hypertension: a phase 2 randomized placebo-controlled study," *Journal of the American Heart Association*, vol. 6, no. 11, 2017.
- [23] A. Sezai, K. Obata, K. Abe, S. Kanno, and H. Sekino, "Cross-over trial of febuxostat and topiroxostat for hyperuricemia with cardiovascular disease (TROFEO trial)," *Circulation Journal*, vol. 81, no. 11, pp. 1707–1712, 2017.
- [24] Y. Ohta, A. Ishizuka, H. Arima et al., "Effective uric acid-lowering treatment for hypertensive patients with hyperuricemia," *Hypertension Research*, vol. 40, no. 3, pp. 259–263, 2017.
- [25] S. Beddhu, R. Filipowicz, B. Wang et al., "A randomized controlled trial of the effects of febuxostat therapy on adipokines and markers of kidney fibrosis in asymptomatic hyperuricemic patients with diabetic nephropathy," *Canadian Journal of Kidney Health and Disease*, vol. 3, no. 1, Article ID 2054358116675343, 2016.
- [26] K.-H. Yu, J.-H. Lai, P.-N. Hsu, D.-Y. Chen, C.-J. Chen, and H.-Y. Lin, "Safety and efficacy of oral febuxostat for treatment of HLA-B*5801-negative gout: a randomized, open-label, multicentre, allopurinol-controlled study," *Scandinavian Journal of Rheumatology*, vol. 45, no. 4, pp. 304–311, 2016.
- [27] D. Sircar, S. Chatterjee, R. Waikhom et al., "Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: a 6-month, double-blind, randomized, placebo-controlled trial," *American Journal of Kidney Diseases*, vol. 66, no. 6, pp. 945–950, 2015.
- [28] S. Tani, K. Nagao, and A. Hirayama, "Effect of febuxostat, a xanthine oxidase inhibitor, on cardiovascular risk in hyperuricemic patients with hypertension: a prospective, open-label, pilot study," *Clinical Drug Investigation*, vol. 35, no. 12, pp. 823–831, 2015.
- [29] K. Tanaka, M. Nakayama, M. Kanno et al., "Renoprotective effects of febuxostat in hyperuricemic patients with chronic kidney disease: a parallel-group, randomized, controlled trial," *Clinical and Experimental Nephrology*, vol. 19, no. 6, pp. 1044–1053, 2015.

- [30] Y. Tsuruta, K. Kikuchi, Y. Tsuruta et al., "Febuxostat improves endothelial function in hemodialysis patients with hyperuricemia: a randomized controlled study," *Hemodialysis International*, vol. 19, no. 4, pp. 514–520, 2015.
- [31] S. Xu, X. Liu, J. Ming et al., "A phase 3, multicenter, randomized, allopurinol-controlled study assessing the safety and efficacy of oral febuxostat in Chinese gout patients with hyperuricemia," *International Journal of Rheumatic Diseases*, vol. 18, no. 6, pp. 669–678, 2015.
- [32] X. Huang, H. Du, J. Gu et al., "An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia," *International Journal of Rheumatic Diseases*, vol. 17, no. 6, pp. 679–686, 2014.
- [33] A. Sezai, M. Soma, K.-I. Nakata et al., "Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD)," *Journal of Cardiology*, vol. 66, no. 4, pp. 298–303, 2015.
- [34] K. Naoyuki, F. Shin, H. Toshikazu et al., "An allopurinol-controlled, multicenter, randomized, open-label, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 2 exploratory clinical study," *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*, vol. 17, no. 4, pp. S44–S49, 2011.
- [35] N. Kamatani, S. Fujimori, T. Hada et al., "Placebo-controlled double-blind dose-response study of the non-purine-selective xanthine oxidase inhibitor febuxostat (TMX-67) in patients with hyperuricemia (including gout patients) in Japan: late phase 2 clinical study," *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*, vol. 17, no. 4, pp. S35–S43, 2011.
- [36] K. Naoyuki, F. Shin, H. Toshikazu et al., "Placebo-controlled, double-blind study of the non-purine-selective xanthine oxidase inhibitor Febuxostat (TMX-67) in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study," *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*, vol. 17, no. 4, pp. S19–26, 2011.
- [37] N. Kamatani, S. Fujimori, T. Hada et al., "An allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study," *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*, vol. 17, no. 4, pp. S13–S18, 2011.
- [38] M. A. Becker, H. R. Schumacher, L. R. Espinoza et al., "The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial," *Arthritis Research & Therapy*, vol. 12, no. 2, article no. R63, 2010.
- [39] M. A. Becker, H. R. Schumacher, P. A. MacDonald, E. Lloyd, and C. Lademacher, "Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout," *The Journal of Rheumatology*, vol. 36, no. 6, pp. 1273–1282, 2009.
- [40] H. R. Schumacher Jr., M. A. Becker, R. L. Wortmann et al., "Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial," *Arthritis Care & Research*, vol. 59, no. 11, pp. 1540–1548, 2008.
- [41] M. A. Becker, H. R. Schumacher Jr., R. L. Wortmann et al., "Febuxostat compared with allopurinol in patients with hyperuricemia and gout," *The New England Journal of Medicine*, vol. 353, no. 23, pp. 2450–2461, 2005.
- [42] M. A. Becker, H. R. Schumacher Jr., R. L. Wortmann et al., "Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout," *Arthritis & Rheumatism*, vol. 52, no. 3, pp. 916–923, 2005.
- [43] A. Nakagomi, Y. Saiki, S. Noma et al., "Effects of febuxostat and allopurinol on the inflammation and cardiac function in chronic heart failure patients with hyperuricemia," *IJC Metabolic and Endocrine*, vol. 8, pp. 46–55, 2015.
- [44] K. G. Saag, A. Whelton, M. A. Becker, P. MacDonald, B. Hunt, and L. Gunawardhana, "Impact of febuxostat on renal function in gout patients with moderate-to-severe renal impairment," *Arthritis & Rheumatology*, vol. 68, no. 8, pp. 2035–2043, 2016.
- [45] Critical Appraisal Skills Programme, "Critical Appraisal Skills Programme (2018). CASP Randomised Controlled Trial Checklist," 2018.
- [46] Coxib and traditional NSAID Trialists' (CNT) Collaboration, N. Bhalra, J. Emberson, A. Merhi et al., "Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials," *Lancet*, vol. 382, pp. 769–779, 2013.
- [47] C. M. T. Greenwood, J. P. Midgley, A. G. Matthew, and A. G. Logan, "Statistical issues in a metaregression analysis of randomized trials: Impact on the dietary sodium intake and blood pressure relationship," *Biometrics*, vol. 55, no. 2, pp. 630–636, 1999.
- [48] I. Holme, A. H. Aastveit, N. Hammar, I. Jungner, and G. Walldius, "Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417 734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS)," *Journal of Internal Medicine*, vol. 266, no. 6, pp. 558–570, 2009.
- [49] H. Huang, B. Huang, Y. Li et al., "Uric acid and risk of heart failure: a systematic review and meta-analysis," *European Journal of Heart Failure*, vol. 16, no. 1, pp. 15–24, 2014.
- [50] J. Wang, T. Qin, J. Chen et al., "Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies," *PLoS ONE*, vol. 9, no. 12, Article ID e114259, 2014.
- [51] D. I. Feig, D. H. Kang, and R. J. Johnson, "Medical progress: uric acid and cardiovascular risk," *The New England Journal of Medicine*, vol. 359, no. 17, pp. 1811–1821, 2008.
- [52] M. M. Givertz, K. J. Anstrom, M. M. Redfield et al., "Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: The xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study," *Circulation*, vol. 131, no. 20, pp. 1763–1771, 2015.
- [53] H. R. Schumacher Jr., M. A. Becker, E. Lloyd, P. A. MacDonald, and C. Lademacher, "Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study," *Rheumatology (Oxford)*, vol. 48, no. 2, pp. 188–194, 2009.
- [54] C. Patrono and C. Baigent, "Nonsteroidal anti-inflammatory drugs and the heart," *Circulation*, vol. 129, no. 8, pp. 907–916, 2014.
- [55] E. Krishnan, "Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout," *Rheumatology*, vol. 49, no. 7, pp. 1229–1238, 2010.

- [56] J. M. Zimmet and J. M. Hare, "Nitroso-redox interactions in the cardiovascular system," *Circulation*, vol. 114, no. 14, pp. 1531–1544, 2006.
- [57] C. Gersch, S. P. Pali, K. M. Kim, A. Angerhofer, R. J. Johnson, and G. N. Henderson, "Inactivation of nitric oxide by uric acid," *Nucleosides, Nucleotides and Nucleic Acids*, vol. 27, no. 8, pp. 967–978, 2008.
- [58] Y.-J. Choi, Y. Yoon, K.-Y. Lee et al., "Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis," *The FASEB Journal*, vol. 28, no. 7, pp. 3197–3204, 2014.